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Article

Obligations, precautions and pending issues in regulatory development for radiopharmaceuticals in Brazil

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Radiopharmaceuticals are compounds that have a radionuclide and may be gamma-radiation emitter (γ) or positrons emitter (β+), linked to a molecule with specific diagnostic and therapeutic purposes**.** The progress in the use of radiopharmaceuticals has culminated to a sector in common with other types of drugs: regulation and surveillance. From 2006 on, production, marketing and use of these drugs were open to the Brazilian market granting much more freedom due to the Constitutional Amendment 49, resulting from the previous Constitutional Amendment 199/03 which removes the Union monopoly for this kind of manipulation and granted this production to other nuclear medicine. From this date on, the amount of this type of sold product have been greatly increased, and the nucleus of surveillance and regulation in Brazil have also advanced in the legislative processes, creating documents that are now more focused on radiopharmaceuticals in the national territory (Resolutions No. 63 and No. 64). In international overview, there is too much to be done in regulatory terms in Brazil, such as adding mainly issues of drugs surveillance to pharmacovigilance practice in radiopharmaceuticals drugs.

Uniterms: Radiopharmaceuticals/regulation. Radiopharmaceuticals/ surveillance.Radiopharmaceuticals/ pharmacovigilance.Pharmacovigilance/practice in radiopharmaceuticals drugs. Brazilian legislation/ radiopharmaceuticals control.

Radiofármacos são compostos que possuem um radionucleotídeo, podendo ser emissor de radiação gama (γ) ou emissor de pósitrons (β+), ligado a uma molécula específica com finalidade diagnóstica e terapêutica. O avanço no uso dos radiofármacos tem culminado a um setor em comum com outros tipos de medicamentos: a regulamentação e fiscalização. Após 2006, a produção, a comercialização e a utilização destes medicamentos foram abertas ao mercado interno brasileiro com maior liberdade, pois a Emenda Constitucional 49, vinda da Emenda Constitucional 199/03, que retira da União o monopólio deste tipo de manipulação, ofereceu a outros centros de medicina nuclear a oportunidade desta produção. A partir desta data, a quantidade comercializada deste tipo de medicamento aumentou absurdamente e os núcleos de vigilância e regulamentação do Brasil avançaram também nos processos legislativos, criando os documentos mais voltados a Radiofármacos existentes no território nacional, as Resoluções n° 63 e n° 64. Em visão internacional, há muito ainda a ser feito em termos regulatórios no Brasil somando principalmente os assuntos vigilantes dos medicamentos como a prática de Farmacovigilância em Radiofármacos.

Unitermos: Radiofármacos/regulamentação. Radiofármacos/fiscalização. Radiofármacos/ farmacovigilância. Farmacovigilância/prática em radiofármacos. Legislação brasileira/controle de radiofármacos.

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INTRODUCTION

The Nuclear Medicine is the specialty of medicine that uses marked radionuclides – radiopharmaceuticals – with therapeutic and diagnostic purposes. It is a procedure that allows anatomical, morphological, physiological and functional evaluations of organs and tissues.

Radiopharmaceutical agent is any medicinal product which, by its pharmaceutical form, quantity and quality of radiation emitted can be used in the diagnosis and treatment of illnesses of living beings, regardless its route of administration (Araújo, 2001). The first use of radiopharmaceuticals in humans occurred in 1927, when Blumgart and Yens (1926) measured the human blood circulation after injection of a saline solution exposed to Radon. Later, studies as Hertz Robert, Evans (1938) on the function of the thyroid gland with the use of iodine-131 marked the beginning of the systemic use.

The radiopharmaceuticals comprise the radionuclide generators, the sets of reactive lyophilized to mark with Technetium-99 m or Kits and the precursors of radiopharmaceuticals. The radionuclide generator is a system of production of radiopharmaceuticals where uses a radionuclide of long half-life that fades away in another radionuclide which elutes (or obtained by methods of extraction) for the preparation of radiopharmaceutical

The kits for the preparation of radiopharmaceuticals may be lyophilized compounds non-radioactive to be reconstituted and/or combined with radionuclides. As for the precursors of radiopharmaceuticals, these can be any radionuclide produced by radio-labeling of a substance, before administration (International Pharmacopoeia, 2004).

The most common radiopharmaceuticals used in diagnosis are in their majority the marked with Technetium-99m (80% of all procedures in Nuclear Medicine) and positron emitters, in particular the Fluoride-18, that are being used in PET-CT technology (Positron Emission Tomography - Computed Tomography). The revolutionary system PET-CT unites the diagnostic resources of Nuclear Medicine (PET) and Radiology (CT), acting through an overlap of metabolic and anatomical images, generating images whole body capable of revealing early malignant lesions (Robilotta, 2006).

In therapeutic use radioisotopes are used to emit beta particles (or alpha), these particles release high power energy to reach tissues/cells and cause cell death. The main beta emitters used are Iodine-131, Lutetium Isotope 177, Itrium-90 and samarium-153.

In Nuclear Medicine the radiopharmaceuticals for use in diagnosis and therapy are generally produced artificially in particle accelerators or reactors, being also accessible through generators of radioisotopes.

These generators allow the use of radionuclide half-life time (T1/2) short, through the decay of a radionuclide with T1/2 long, the latter being produced in reactors or ciclotrons. There is also the radionuclides which decays by emission of β- particles which are produced in reactor by fission of ^{235}U (Uranium235) or by neutron capture reactions (n,γ or n,p) in a sample of appropriate target.

On the other hand, the radionuclides which decay by electronic capture or emission of β+ particles are produced in cyclotrons, where the particles of high energy interact with stable nuclei of certain targets, giving rise to products handicapped in protons. In this process, the particles that interact with the target samples may be protons, deuterons, α-particles or 3He (Oliveira *et al*, 2006).

The progress in the area of obtaining images through the use of radiopharmaceuticals demanded a more specific Brazilian regulation and also more properly regarding the parameters of safety, quality and efficacy.

Currently, Brazilian law provides two Resolutions, RDC 63 and 64/2009, published exclusively for radiopharmaceuticals (Brasil, 2009a,b).

Thus, the objective of this review article is to describe the normative aspects involving radiopharmaceuticals with emphasis in Resolutions no. 63 and 64, 2009, and prepare a brief evolution of global regulation of this therapeutical class.

PHARMACOVIGILANCE

The Pharmacovigilance is a required field of importance facing the health and should be performed by every holder of record of medicine.

The activities include the detection, evaluation and prevention of adverse reactions or problems from medications (Brazil, 2009c).

In 1989 it was recommended to the National System of Health Surveillance to establish an efficient system of Pharmacovigilance track Resolution of the National Council of Health, and then, actions of pharmacovigilance actions were included as an aid to promote rational use of medicines (Brazil 1998).

However, only in 2003 the Unit of Pharmacovigilance disclosed information pertinent to the leaflet of radiopharmaceuticals and the paramount importance of informational reports for the renewal of medicines. After the designated Management Pharmacovigilance, in 2007, there were Resolutions to standardize and assist this whole process, which today, is indispensable to any holder of record of medication as provided in RDC nº 4 of February 10, 2009 (Brazil, 2009c).

LEGISLATION

International Legislation

The regulations of radiopharmaceuticals initially established in the USA and Europe has gained attention of other producer countries of this therapeutic class, however, with a deficit of legislation. From the beginning, the USA and Europe have a solid legislation on radiopharmaceuticals.

USA

In the United States, the Constitutional Amendment of 1938 first appeared with the intention of regulating this new therapeutic class. In 1944, the Department of Biological Products the Food and Drug Administration (FDA) has taken over the regulation of radiopharmaceuticals as biological component and, by presenting radioactive properties, for a long time they were also controlled by Atomic Energy Commission (AEC). In 1954, the AEC was authorized to license the ownership, the use and transfer of materials considered by-products which included the radiopharmaceuticals. In 1963, the FDA allowed a temporary exemption for new radioactive and biological drugs regarding regulatory requirements for new investigational drugs, called Investigational New Drug (IND). In 1971, this exemption was annulled, passing to effective the regulatory requirements for Application of New Medicines, called Application New Drugs (NDA) for radiopharmaceuticals (Petry, 1989). In 1989, the FDA approved the radiopharmaceutical 82Rb - Rubidium chloride for the Evaluation of Myocardial Perfusion. In 1997, the president of the United States has decreed that the FDA was component responsible for describing the procedures and Good Manufacturing Practices (GMP) for radiopharmaceuticals used in PET (Oliveira, 2008). The GMP for medicinal products in general are described in the Code of Federal Regulations (FRC), title 21, parts 210 and 211 part 212 specifically, describes the GMP of radiopharmaceuticals PET because they are considered by the FDA a particular type of radiopharmaceuticals. In 1998, it was added to the FRC 21, part 315, which refers to the regulation of radiopharmaceuticals for use *in vivo* diagnosis and monitoring.

Moreover, part 601 on License presents a sub-part D (601.30 to 601.35) which specifically refers to radiopharmaceuticals (Araújo *et al.,* 2008). The CFR title 10, chapter I, parts 1-199, is specifically dedicated to the Nuclear Regulatory Commission (NRC). While, many sections are applied to the practice of Nuclear Medicine, however the parties 20 (Standard is Protection against Radiation) and 35 (Medical Uses of Byproduct Material) are the most referenced when it comes to radiopharmaceuticals.

In 2000 three radiopharmaceuticals with diagnostic purposes were approved by the FDA, namely: the 18F - Sodium fluoride for bone scans, the 18F- Fluordesoxiglucose for use in oncology and assessment of myocardial viability and 13N-Nitrogen for evaluation of myocardial blood flow (Petry, 2004). Currently, the regulation and fiscalization of radiopharmaceuticals and medical equipment used in nuclear medicine are controlled by the FDA while the aspects related to radiation are controlled by the NRC. Other federal regulatory agencies such as Occupational Safety and Health Administration (OSHA), Environmental Protection Agency (EPA) and Department of Transportation (DOT) regulate the safety in industrial production, storage and of radiopharmaceuticals transportation.

Europe

The legal acts that culminated in regulation of radiopharmaceuticals in Europe were the directives published in 1986 and in 1989 (Oliveira, 2008). These directives were reviewed and updated over the years. In 1991, the European Commission published the Directive 91 /356/EEC that regulates in those GMP medicinal products for human use. Annex 3 which is part of the GMP guide is related to the production of radiopharmaceuticals, including topics such as installation, human resources, documentation, equipment, quality control and distribution. This Annex applies to radiopharmaceuticals, PET radiopharmaceuticals, radioactive precursors for the production of radiopharmaceuticals and radionuclide generators (Araújo *et al.*, 2008). The last update of this attachment was in March 2009. When there is some clinical research about radiopharmaceuticals, this will be considered as investigational product and must be produced in accordance with the principles of EudraLex (Rules and Government Regulations Medicines European Union), Volume 4 (Good Manufacturing Practice - GMP).

In the meantime, the European Association of Nuclear Medicine (EANM) has created a guide for the production of radiopharmaceuticals which is divided into product prepared from lyophilized reagents for tagging, PET radiopharmaceuticals and other locally produced (Araújo *et al.,* 2008).

National Legislation

In Brazil, the term Radiopharmaceuticals appeared

for the first time in 1988 in the Brazilian Pharmacopoeia (Oliveira, 2008). In 1999 it was published the Law 9.782/99 that says "*Art 8: Delegate to the agency to regulate, control and supervise the products and services that involve risk to public health: IX - radioisotopes for in vivo diagnostic radiopharmaceuticals and radioactive products used in diagnosis and therapy* "(Brazil, 1999). The most recent modification of the Brazilian Constitution of 1988 was due to the change in the wording of paragraph b, adding a paragraph c into the section XXIII of the main clause of Article 21 and the new text of section V of the chapeau of Article 177 (Brazil, 2006).

This term was used again only in 2006 when it created the Subcommittee on Radiopharmacy due to the initiative of the National Commission of Nuclear Energy (CNEN) and the Standing Committee of Revision of the Brazilian Pharmacopoeia (CPRFB). Thus, there was a rupture in the monopoly of production, marketing and use of radioisotopes of short half-life, for medical, agricultural and industrial in Brazil, designed by Constitutional Amendment 49 (Santos-Oliveira, Carneiro, Leão, 2008). Originate from the Proposed Constitutional Amendment 199/03, which removes the Union's the monopoly of manipulation of radioisotopes with short half-life, Constitutional Amendment 49 facilitated the creation of new nuclear medicine centers that offer the service of tomography to the population. The radioisotopes of short half-life are produced by institutes of CNEN (National Commission of Nuclear Energy) as the IEN (Institute of Nuclear Engineering) (Santos-Oliveira, Carneiro-Leão, 2007; Santos-Oliveira, Carneiro-Leão, 2008).

Constitutional Amendment 49 brought a huge advance in Brazilian Radiopharmacy, because through it, it was found a new job market for pharmacists and many other professionals, whose market was previously restricted to institutions of CNEN.

Notwithstanding this fact imposed suddenly the Brazilian pharmacy a new paradigm, with many challenges and obstacles to overcome, starting by regulatory processes (Santos-Oliveira, Carneiro-Leão, 2007).

The subcommittee was responsible for updating the theoretical Pharmacopeia and elaboration of monographs where in 2007, through the Ordinance No. 42 of 25/01/2007 it was established a Working Group composed of representatives of the Agency to develop regulations for the registration and inspection of these products, and on June 4, 2008 was published RDC 38 providing guidelines for the installation and operation of Nuclear Medicine Services "*in vivo*" (Brazil, 2008).

Recently, ANVISA published two specific resolutions for radiopharmaceuticals - the RDC No. 63 of 18 December, 2009 - establishing the minimum requirements for the manufacture and - RDC No. 64 of December 18, 2009 - which describes the process of registration of these medicines (Brasil, 2009a,b).

From this resolution, all radiopharmaceutical for diagnostic or therapeutic use, being restricted to hospitals and clinics shall be registered in Brazil. Besides legislation ANVISA, CNEN published some standards and guidelines where divided into groups, e.g. Group 3: Radiological Protection (NE 3.01 (Brazil, 2005), NE 3:05 (Brazil, 2013), Group 6: Radioactive Facilities (NN 6:01 (Brazil, 1997) and Group 8: Radioactive Tailings NE 8.01 (Brazil, 2014).

RDC NO. 63 OF 18 DECEMBER 2009

Radiopharmaceuticals manufacturing

The requirements of the RDC No. 63, 18 December 2009, intends to supplement the Resolution of Good Manufacturing Practice for Medicinal Products containing topics such as facilities, equipment, personnel, production, Documentation, Quality Assurance and Control. This Resolution provides the minimum requirements for the manufacturing of these products from production in industries and institutions to the preparation itself (Brazil, 2009a).

Santos-Oliveira *et al.* (2008) wrote an article describing the manufacturing and sanitary aspects for the construction of a production line of radiopharmaceuticals.

As RDC no. 63/2009 was in published only in 2009, by the year of publication of this Article, the authors based its content on the following documents: guidelines on standards of national and international quality referred to GMP for injectable medications; RDC 210/03 that is referred to the GMP applied to medicines in general and on standards of radiological protection and safety and security of workplace.

Thus the authors concluded that the development of industrial projects in this area based on these laws was impracticable for being radioactive medicinal product. For this reason too, the publication of the RDC no. 63/2009 was of extreme importance in supporting and to supplying the information deficit regarding to the manufacture of radiopharmaceuticals (Brazil, 2009a).

RDC NO. 64 OF DECEMBER, 18th – 2009

Radiopharmaceuticals registration

RDC No. 64 of December 18, 2009 establishes all the steps to be followed for obtaining registration of

medications for both diagnostic and therapeutic use. The Chapter on Registry of such legislation is divided into three (3) sub-chapters: Chapter I: Initial Provisions, Chapter II: Imported Products and Chapter III: Registration Renewal. Chapter I has eight (8) sections such as: Section I: Background Measurements to the registry; Section II: Registration Documentation; Section III: Report on Clinical Efficacy and Safety; Section IV: Technical Report, Section V: Production Report and Quality Control, Section VI: Shelf Life; Section VII: Leaflet Text and Section VIII: Label Packaging Primary and Secondary. Furthermore, this resolution has two annexes, Annex I: Active Principles of Radiopharmaceuticals for Customary Use Annex II: Clinical Information Specific to the Radiopharmaceuticals Diagnostic (Brazil, 2009b).

The present Resolution establishes criteria for clinical studies of radiopharmaceuticals performed prior to their registration. In addition, manufacturers of radiopharmaceuticals should present pharmacovigilance reports (Brazil, 2009b).

The composition of the radiopharmaceutical agent, its half-life, as well as its properties, toxicology and physicochemical characteristics are required information mandatory for the register (Brazil, 2009b).

FINAL CONSIDERATIONS

The treatment with radiopharmaceuticals grows at a rate of 10% per year. In 2002, approximately 2 million patients were treated at 278 hospitals and clinics throughout Brazil. In the United States, one-third of hospitalized patients receive some treatment with radiopharmaceutical (Regis, 2002). The benefits these patients enjoy are, mainly, regarding to early diagnosis of cancer, heart disease, neurological and much less invasive treatment and more effective in terms of tumors.

Radiopharmaceuticals are drugs of immediate effects. And with the objective of promoting the right of patients to have the life quality assured, every Brazilian citizen has his/her rights entitled to be respected by means of an efficient and responsible monitoring team set up.

In 2006, the monopoly of the manufacturer and marketing of radiopharmaceuticals was broken in Brazil and a prominent opportunity was perceived for new companies with innovative context for research and medications. When it comes to clinical history there is a lack of new studies, and there is a deficiency of new studies, researchers in this area and surveillances services too. In this sense, the publication of specific resolutions in the area is a major breakthrough for Brazil.

The resolutions are clear setting the term of 2 (two) years from the date of its publication for companies adaptation to the Technical Regulations (Brasil, 2009a,b). But, in December, 2011 was published RDC No. 66 which extended for over two years that any company producing radiopharmaceuticals technically adapt and follow the GMP of these drugs. Furthermore, this RDC also extended for three years the registration of the pertaining documents and maintenance and renewal of registration itself (Brazil, 2011).

Brazil needs to engage in the arduous surveillance of new technologies such as radiopharmaceuticals. Thus, it can enable innovation in benefit of Brazilian health, where early diagnosis is just only one of several important tools within research that need to be available soon.

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